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Limited Access to Ethanol in Genetic Drinking Rats Is Suppressed While Feeding Is Enhanced by the Mixed 5-HT_{1A} Agonist/5-HT_{2A} Antagonist FG5938

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WEST, M. W., G. KALMUS AND R. D. MYERS. *Limited access to ethanol in genetic drinking rats is suppressed while feeding is enhanced by the mixed 5-HT_{1A} agonist/5-HT_{2A} antagonist FG5938.* PHARMACOL. BIOCHEM. BEHAV **60**(4) 823–828, 1998—Serotonin (5-HT) receptor agonists, antagonists, and mixed agonist/antagonists have been implicated in the volitional intake of ethanol in the rat and other species. The present experiments were undertaken to determine whether FG5938 (1-[4-(*p*-fluorophenyl)butyl]-4-(6-methyl-2-pyridinyl)-piperazine fumarate) would alter ethanol drinking in: genetic ethanol preferring (P) rats; and a new strain of high ethanol preferring (HEP) male and female rats derived from crossbreeding of P and a variant strain of Sprague–Dawley animals. After a preference test for solutions of 3 to 30% ethanol vs. water, each rat was given limited access to its maximally preferred concentration daily between 1600 and 1800 h; fluid intakes were recorded every 0.25 h. Once fluid consumption had stabilized over 4 days, saline vehicle, 2.5 mg/kg or 5.0 mg/kg FG5938 was injected subcutaneously 0.5 h prior to ethanol access on each of 3 consecutive days; thereafter, preference testing for ethanol continued for 4 additional days. Whereas the saline vehicle was without effect, FG5938 caused a fivefold decrease in total intake of ethanol from 1.7 to 0.3 g/kg and in proportion of ethanol to total fluid consumed from 0.42 to 0.03. The onset of the significant decline in ethanol drinking occurred during the latter 1.75-h interval. Further, both doses of FG5938, but not saline, increased the intake of food significantly. The decline in ethanol drinking was virtually identical in both P and HEP males and in female HEP rats. These results demonstrate that FG5938 affects ethanol drinking only after 0.5 h of its administration. Finally, it is envisaged that the ingestion of ethanol in genetic high drinking rats is mediated, in part, by central synapses utilizing both 5-HT_{1A} and 5-HT_{2A} receptors. © 1998 Elsevier Science Inc.

Ethanol drinking Serotonin Brain Alcohol intake Ethanol preference 5-HT_2 receptors Alcoholism 5-HT_{1A} receptors

CEREBRAL serotonin (5-HT) has been implicated historically in the etiology of the excessive drinking of ethanol (16,21,24). In the brain of the naive ethanol-preferring (P) rat, for example, the innate level of 5-HT is much lower and density of 5-HT_{1A} receptors is higher than in the nonpreferring (NP) rat (33). Thus, a functional impairment of central 5-HT systems in high ethanol-drinking animals could predispose an individual to drink copious amounts of ethanol (25,28). Consequently, the specific level of 5-HT in the brain is believed to determine, in part, the nature of the volitional consumption of ethanol (19,28). An upregulation or downregulation of serotonergic receptors in relation to the amount of available 5-HT can also influence the preference or avoidance of ethanol in an experimental animal (1,6,11,33). Thus, a pharmacological intervention that effectively shifts the level or activity of 5-HT in the brain has been suggested as a strategy to ameliorate abnormal drinking (23), as illustrated by the effects of 5-HT reuptake inhibitors such as zimelidine, citalopram, and sertra-

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line on ethanol preference in rats (23,25). However, a reduction in ethanol intake is typically accompanied by untoward side effects of the respective drug including declines in body weight, food, and water intakes (2,9,25).

Recently, it was shown that the chronic or acute administration of FG5606 (amperozide), a 5-HT_{2A} receptor antagonist (10), can suppress ethanol intake long after its discontinuation, and with no apparent side effects, in genetically predisposed or chemically induced drinking rats (23,26). Further, a series of mixed 5-HT_{1A} agonist/5-HT_{2A} antagonists, FG5938, FG5893, and FG5865, also reduce ethanol consumption in genetic or chemically induced drinking rats, again without affecting food or water intake significantly (17,23,30,32). One of these drugs, FG5938, acts to enhance food intake concurrently with the decline in ethanol preference (30), a unique effect that has not been reported previously. The affinity values of this monophenylbutyl derivative for 5-HT_{1A} and 5-HT_{2A} receptors are K_i = 0.9 nM and K_i = 10.0 nM, respectively (A. Björk, personal communication). The rationale for this study, therefore, was to determine whether this uncommon action of FG5938 would occur also when the genetic ethanol drinking rat was provided only a limited interval of access to ethanol. By use of this paradigm, the pharmacokinetic profile of action of FG5938 could be estimated by recording fluid intakes at 0.25-h intervals over a 2-h test period.

For these experiments, two rat lines of genetic drinkers were used: male ethanol-preferring (P) rats, and a new strain of male and female high ethanol-preferring (HEP) rats derived from crossbreeding P rats with ethanol drinking Harlan–Sprague–Dawley female rats (27). These animals were selected because they maintain their respective high g/kg and proportional intakes of ethanol, in contrast to other genetic drinkers, in the presence of both a highly palatable chocolate solution or nonnutrient sweet solution (14,15,27).

METHOD

Adult male P rats (n = 8) and male (n = 4) and female (n = 4) high ethanol-preferring (HEP) rats, derived from crossbreeding P rats with high drinking Sprague–Dawley females (27), were housed individually in stainless steel wire mesh cages at an ambient temperature of 22 to 24°C and on a 12-h illumination cycle with lights on at 1600 h. Although fluids were restricted to 2 h daily, Agway NIH formulation rodent chow was available ad lib. to the rats with their respective intakes and body weight recorded daily at 0800 to 0900 h. All experimental procedures used for these studies were approved by the Animal Care and Use Committee of the School of Medicine and were in strict compliance with the National Institutes of Health guidelines for the care and use of laboratory animals.

Determination of Ethanol Preference

The preferred concentration of ethanol for each rat was determined by means of a standard three-bottle, two-choice procedure carried out over 10 days (14,21). Three 100 ml Kimax drinking tubes were placed equidistantly on the front of each cage: one tube contained a v/v solution of ethyl ethanol (U.S. Pharmacopeia) in tap water, the second contained tap water, and the third remained empty. The tubes were rotated daily to deter the development of a position habit (15,21).

The necessity for the screening of preference for ethanol over a range of concentrations from low to high has been well documented scientifically since the 1970s (21). In fact, the arbitrary selection by an investigator of a single concentration such as 10% ethanol does not reflect validly an individual animal's actual choice of a percent concentration of ethanol that is maximally consumed over all others. As an example from the literature, the mean percent ethanol solution preferred by P rats over all other concentrations from 3 to 30% is 25%, with a mean intake of 10.9 g/kg per day, whereas HAD rats prefer 20% with a mean intake of 10.6 g/kg per day (14,15).

In this study, 3% ethanol was offered on the first test day; then on each day thereafter the concentration of ethanol was increased as follows: 4, 5, 7, 9, 11, 13, 15, 20, and 30%. At the end of this preference test, the maximally preferred solution of ethanol was determined individually for each rat as based on the highest intake of ethanol in absolute g/kg per day when the proportion of ethanol to total fluid remained at the 0.5 level. Thereafter, this concentration of ethanol was offered together with water to each rat for the remainder of the experiment. In this case, the preferred ethanol concentrations were as follows: overall mean of 14.8% for all 16 rats; mean of 16% for the P rats (range 13 to 20%), mean of 14% for the male HEP rats (range 11 to 15%), and mean of 13% for the female HEP rats (range of 11 to 15%).

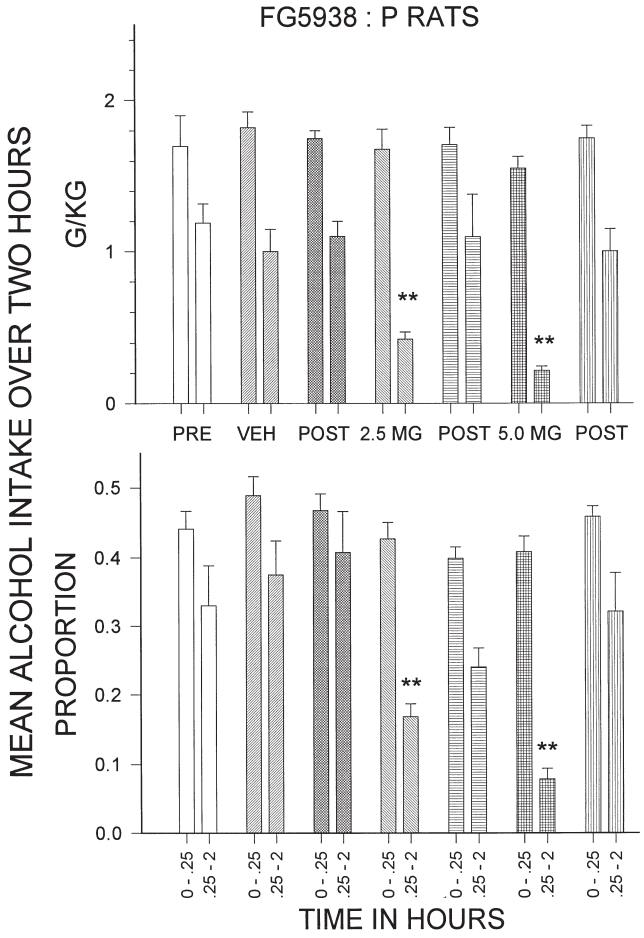

FIG. 1. Mean ± SE alcohol intakes of male P rats in terms of absolute g/kg (top) and proportion of alcohol to total fluid consumed (bottom) at timed intervals of 0–0.25 and 0.25–2 h during: 4 days preinjection (PRE), 3 days subcutaneous injection of saline vehicle (VEH), 2.5 mg/kg or 5.0 mg/kg of FG5938; and 4 days of posttreatment (POST). n = 8. **p <0.01.

Limited Access Paradigm

Each rat was given access to its preferred ethanol solution and water daily between 1600 to 1800 h. The intakes of both fluids were recorded initially and then measured every 0.25 h throughout the 2.0-h access interval. A 2-week period of acclimatization was required to establish baseline values of ethanol and water consumed during this period. Baseline drinking of each fluid was considered to have stabilized when the intakes of ethanol and water varied by less than 15% above or below the mean amounts ingested over successive 4-day periods.

Administration of FG5938

FG5938 for injection was prepared daily in sterilized 0.9% saline and sonicated in a warm bath to facilitate its dissolution. Following a 4-day control baseline period, 2.5 mg/kg, 5.0 mg/kg, or the control saline vehicle was injected subcutaneously in each rat at 1530 h. The rationale for administering the drug 30 min prior to ethanol was based on pilot data on the pharmacokinetics of the drug that showed its latency of action. Testing for ethanol preference during limited access continued during these 3 consecutive days of treatment and for an additional 4 days thereafter. Following a counterbalanced design, this 11-day sequence was repeated twice so that each rat was given each injection regimen as follows: 2.5 mg/kg (n = 16), 5.0 mg/kg (n = 16) and saline control (n = 16).

Data Analyses

The data were analyzed by computer using SigmaStat software (Jandel Scientific). The mean and SE intake of ethanol, in g/kg and proportion of ethanol to total fluid consumed as well as daily food and water intakes and body weights were calculated for all groups over 2 h for the baseline pretest, injection sequence, and the posttest periods. The mean and SE values were calculated for fluid intakes over each 0.25-h interval in terms of g/kg and water consumed during baseline, injection, and postinjection intervals. The proportion of ethanol to total fluid intake was also calculated to serve as an index of overall preference for ethanol over water and to crossvalidate the absolute level of ethanol consumed (15,21). Repeated-

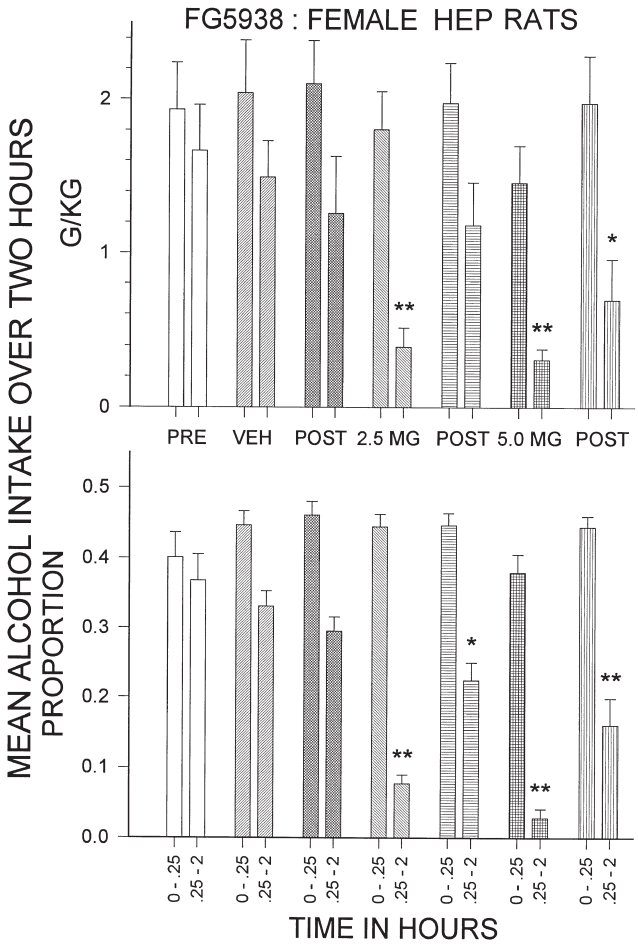

FIG. 2. Mean ± Se alcohol intakes of female HEP rats in terms of absolute g/kg (top) and proportion of alcohol to total fluid consumed (bottom) at timed intervals of 0–0.25 and 0.25–2 h during: 4 days preinjection (PRE), 3 days subcutaneous injection of saline vehicle (VEH), 2.5 mg/kg or 5.0 mg/kg of FG5938; and 4 days of posttreatment (POST). n = 4. *$p < 0.05$; **$p < 0.01$.

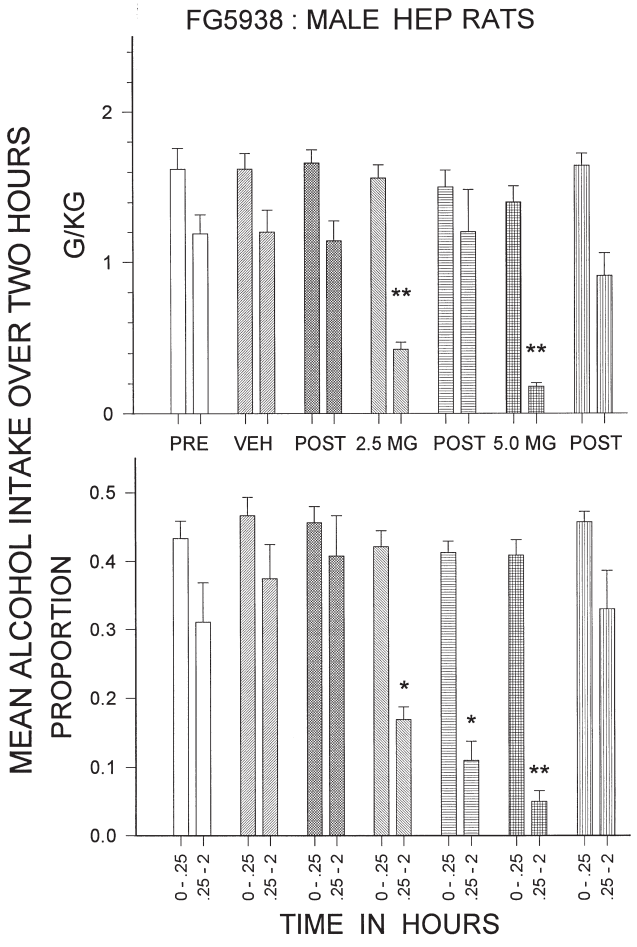

FIG. 3. Mean ± SE alcohol intakes of male HEP rats in terms of absolute g/kg (top) and proportion of alcohol to total fluid consumed (bottom) at timed intervals of 0–0.25 and 0.25–2 h during: 4 days preinjection (PRE), 3 days subcutaneous injection of saline vehicle (VEH), 2.5 mg/kg or 5.0 mg/kg of FG5938; and 4 days of posttreatment (POST). n = 4. **$p < 0.01$.

measures analyses of variance were preformed on all data; a p-value of <0.05 was considered statistically significant.

RESULTS

FG5938 administered in doses of 2.5 and 5.0 mg/kg did not affect significantly the absolute g/kg and proportional intakes of ethanol during the initial 0.25-h access to the fluid in either male P rats or high drinking male and female crossbred HEP rats. Because the decline in the rate of drinking varied substantially among animals, over each of the remaining seven 15-min intervals, the data for the remaining 1.75 h access were grouped for all rats. During this interval, the g/kg intakes of ethanol declined from a pretreatment level of 1.23 ± 0.10 to 0.42 ± 0.04 g/kg during treatment of all groups with the lower dose, $F(1, 31) = 42.1$, $p < 0.01$, and to 0.19 ± 0.02 g/kg during injections of the higher dose, $F(1, 31) = 72.9$, $p < 0.01$. Similarly, FG5938 suppressed significantly the proportional values during the latter 1.75-h ethanol access from 0.38 ± 0.03 to 0.13 ± 0.01, $F(1, 31) = 61.2$, $p < 0.01$, and to 0.07 ± 0.01, $F(1, 31) = 99.1$, $p < 0.01$, during administration of the lower and higher doses of the drug, respectively. During the post drug interval, the g/kg was still suppressed by the high dose of FG5938, $F(1, 31) = 13.9$, $p < 0.01$, whereas the proportional values were reduced by both the low and high doses of the drug, $F(1, 31) = 6.2$, $p < 0.01$, and $F(1, 31) = 11.1$, $p < 0.01$, respectively.

Response to FG5938 of P Rats

As shown in Fig. 1, the g/kg and proportional intakes of ethanol again were unaffected by FG5938 over the initial 0.25 hr interval. However, FG5938 suppressed g/kg intakes over the remaining 1.75 h access to ethanol from 1.19 ± 0.13 to 0.43 ± 0.05, $F(1, 15) = 31.2$, $p < 0.01$, and to 0.22 ± 0.03, $F(1, 15) = 55.5$, $p < 0.01$, during injections of the lower and higher doses, respectively. The proportional values declined correspondingly from 0.34 ± 0.06 to 0.17 ± 0.01, $F(1, 15) = 38.5$, $p < 0.01$, and to 0.08 ± 0.01, $F(1, 15) = 58.8$, $p < 0.01$, during administration of the lower and higher doses, respectively (Fig. 1). The g/kg and proportional intakes of ethanol during the 4 posttreatment days returned to their pretreatment levels.

Response to FG5938 of HEP Rats

In high-drinking female crossbred HEP rats, FG5938 also failed to affect the initial 0.25-h intakes of ethanol. As presented in Fig. 2, the g/kg ethanol consumed during the remaining 1.75-h access declined significantly from 1.67 ± 0.30 to 0.39 ± 0.12 g/kg, $F(1, 7) = 17.1$, $p < 0.01$, and to 0.31 ± 0.12 g/kg, $F(1, 7) = 26.8$, $p < 0.01$, during administration of the lower and higher doses of FG5938, respectively. Concurrently, the proportional values fell from 0.37 ± 0.02 to 0.08 ± 0.02, $F(1, 7) = 14.8$, $p < 0.01$, and to 0.03 ± 0.01, $F(1, 7) = 24.8$, $p < 0.01$, during injections of 2.5 and 5.0 mg/kg FG5938, respectively. During the postdrug interval, the g/kg intake of the females for the remaining 1.75 h was still suppressed by the high dose of FG5938, $F(1, 7) = 5.97$, $p < 0.05$, whereas the proportional values were reduced by both the low and high doses of the drug $F(1, 7) = 9.3$, $p < 0.05$, and $F(1, 7) = 12.8$, $p < 0.01$, respectively (Fig. 2). In the male HEP rats, FG5938 reduced g/kg ethanol ingested (Fig. 3) during the latter 1.75 h access from 1.19 ± 0.13 to 0.43 ± 0.03, $F(1, 7) = 14.5$, $p < 0.01$, and to 0.18 ± 0.02, $F(1, 7) = 26.5$, $p < 0.01$, during treatment with the lower and higher doses, respectively. Similarly, the proportional values decreased from 0.31 ± 0.06 to 0.16 ± 0.01, $F(1, 7) = 6.1$, $p < 0.05$, and to 0.05 ± 0.01, $F(1, 7) = 14.5$, $p < 0.01$, during lower and higher doses of FG5938, respectively (Fig. 3).

TABLE 1

MEAN ± SE FOOD INTAKES (g) OVER 24 H, WATER INTAKES (ml), AND TOTAL FLUID INTAKES (ml) OVER 2-H LIMITED ACCESS TO PREFERRED CONCENTRATIONS OF ALCOHOL OF P RATS (n = 8), MALE HEP RATS (n = 4), AND FEMALE HEP RATS (n = 4)

	Food Intake (g)	Water Intake (ml)	Total Fluid Intake (ml)
P rats (n = 8)			
PRE	20.1 ± 0.6	23.5 ± 1.0	40.1 ± 0.8
FG5938 (2.5 mg/kg)	23.1 ± 0.7*	28.6 ± 1.3*	40.9 ± 1.1
POST	20.9 ± 0.8	24.5 ± 1.1	41.3 ± 1.3
FG5938 (5.0 mg/kg)	23.5 ± 0.8*	30.0 ± 1.2*	39.7 ± 1.2
POST	20.7 ± 0.3	22.3 ± 1.2	40.2 ± 1.0
Male HEP (n = 4)			
PRE	14.5 ± 0.9	15.4 ± 1.2	28.3 ± 1.0
FG5938 (2.5 mg/kg)	16.7 ± 0.9*	19.5 ± 0.8*	29.2 ± 1.1
POST	15.6 ± 0.5	16.5 ± 1.2	29.4 ± 0.9
FG5938 (5.0 mg/kg)	17.4 ± 0.7*	21.3 ± 1.0	29.3 ± 1.1
POST	15.0 ± 0.6	17.4 ± 1.0	29.3 ± 1.1
Female HEP (n = 4)			
PRE	10.9 ± 0.7	11.2 ± 0.9	20.7 ± 1.1
FG5938 (2.5 mg/kg)	13.5 ± 0.8*	14.9 ± 0.7*	21.8 ± 1.0
POST	11.8 ± 1.0	12.5 ± 0.9	22.0 ± 0.8
FG5938 (5.0 mg/kg)	14.4 ± 0.8*	16.7 ± 0.8*	20.4 ± 1.1
POST	11.2 ± 0.7	17.4 ± 0.7*	21.1 ± 0.9

Values represent 4 preinjection days (PRE), 3 days during administration of either 2.5 or 5.0 mg/kg FG5938 and 4-day interval after treatment (POST) *p <0.05.

Body Weight, Food, and Water Intakes

As shown in Table 1, FG5938 enhanced the mean consumption of food and water significantly ($p < 0.05$) in all three groups during the administration of either 2.5 mg/kg or 5.0 mg/kg FG5938. With the exception of female HEP rats, both food and water intakes returned to baseline levels after injections. Further, the body weights of each of the groups of ethanol-preferring rats were not significantly affected by FG5938 given at either dose.

DISCUSSION

The present results show that in a 2-h limited access paradigm in which rats had been fluid deprived for 22 h, FG5938 suppressed ethanol consumption in a dose-dependent manner beginning 45 min or longer after its administration. This relatively long latency in the attenuation of ethanol drinking would suggest that a sufficient level of FG5938 was reached after this period to affect ethanol intake. Further, FG5938 did not produce any apparent untoward side effects such as suppression of food or water intakes or a decline in body weight. In fact, the ingestion of food tended to increase during the administration of either dose of FG5938; in addition, water intake also was high due to the 22-h fluid deprivation. Thus, the attenuation of ethanol drinking caused by FG5938 was not due to a secondary side effect of the drug, i.e., impairment of the central mechanisms governing caloric intake. This finding is in contrast to the action of certain drugs such as zimelidine or sertraline that act centrally on serotonergic neurons to inhibit the reuptake of 5-HT and reduce food intake concomitantly with ethanol drinking (2,9,25).

The mechanisms of action in the suppression of ethanol ingestion by FG5938 most likely are similar to those of FG5893 and FG5865, which possess high affinities to both 5-HT_{1A} and 5-HT_{2A} receptors in the brain (17,30,32). These drugs similarly reduce ethanol consumption in genetic and chemically induced drinking rats, again without affecting food or water intake significantly (17,30,32). In addition, they can alter the characteristics of reuptake and release of 5-HT in serotonergic synapses similar to that of amperozide as well as modify significantly the in vivo efflux of dopamine from different sites in the limbic system of the rat (12,17,29,34). Interestingly, FG5938 may share pharmacological properties similar to those of the 5-HT_{2A} antagonist, amperozide, in attenuating ethanol preference temporally, well after the treatment of the drug is withdrawn, without confounding side effects in genetic-drinking rats (26). The affinity of FG5938 for 5-HT_{1A} receptors may account, in part, for its action on ethanol consumption in that the 5-HT_{1A} agonist, buspirone, likewise diminishes ethanol drinking in the rat and monkey (4,13,31).

The transient increase in feeding observed also in a previous study in rats during the administration of FG5938 (30) would seem to parallel that of another 5-HT_{1A} agonist, 8-OH-DPAT, which enhances food intake and raises the nocturnal metabolic rate in the rat (3). 8-OH-DPAT is thought to act on somatodendritic autoreceptors in the brain stem (8), which reduce 5-HT activity at postsynaptic receptors (7). This would coincide with the concept that a decline in serotonergic function in the forebrain would enhance feeding behavior, whereas an increase in the 5-HT activity would tend to lead to satiety (5).

Interestingly, the male drinking P rats, which possess lower levels of cerebral 5-HT than NP rats (20), as well as male HEP rats showed similar dose-dependent responses to FG5938. However, a maximum suppression in drinking occurred after both doses. The female HEP rats seems to be more reactive to the drug in terms of magnitude as well as prolonged action of FG5938 on ethanol drinking. Although hormonal influences on ethanol drinking could well be a factor, gender differences in response to an alteration in 5-HT receptor function in cerebral structures could underpin the high drinking of ethanol in the female rat genetically bred for this behavior. Thus, it is conceivable that the innate characteristics governing the preference for ethanol in a given strain of variant rat may not necessarily share similar traits in serotonergic functions in mesolimbic and other structures (18,33,35). Additional studies will be required to determine specific neurochemical processes in these rats that may provide insight into the differences of effect of a given 5-HT_1 or 5-HT_2 receptor drug on ethanol preference (22,23).

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